Small molecule screening with laser cytometry can be used to identify pro-survival molecules in human embryonic stem cells.

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Public Summary:
One critical issue that hinders the use of human embryonic stem cells (hESCs) in regenerative medicine, is the poor survival upon dissociation. This limits genetic manipulation of individual hESCs, and also hampers production of large-scale culture of these cells. In this work, we successfully developed a screening platform that allows for large scale screening to identify small molecules that regulate survival. This work validated the use of laser scanning cytometry in a large scale platform for hESC screening. We were able to use this platform to validate existing and discover potential new regulators of survival in hESCs. These small molecules provide targets for both improving our basic understanding of hESC survival as well as a tool to improve our ability to expand and genetically manipulate hESCs for use in regenerative applications.

Scientific Abstract:
Differentiated cells from human embryonic stem cells (hESCs) provide an unlimited source of cells for use in regenerative medicine. The recent derivation of human induced pluripotent cells (hiPSCs) provides a potential supply of pluripotent cells that avoid immune rejection and could provide patient-tailored therapy. In addition, the use of pluripotent cells for drug screening could enable routine toxicity testing and evaluation of underlying disease mechanisms. However, prior to establishment of patient specific cells for cell therapy it is important to understand the basic regulation of cell fate decisions in hESCs. One critical issue that hinders the use of these cells is the fact that hESCs survive poorly upon dissociation, which limits genetic manipulation because of poor cloning efficiency of individual hESCs, and hampers production of large-scale culture of hESCs. To address the problems associated with poor growth in culture and our lack of understanding of what regulates hESC signaling, we successfully developed a screening platform that allows for large scale screening for small molecules that regulate survival. In this work we developed the first large scale platform for hESC screening using laser scanning cytometry and were able to validate this platform by identifying the pro-survival molecule HA-1077. These small molecules provide targets for both improving our basic understanding of hESC survival as well as a tool to improve our ability to expand and genetically manipulate hESCs for use in regenerative applications.